National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Zynteglo for treating transfusion-dependent beta-thalassaemia

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	bluebird bio (company)	The name LentiGlobin no longer applies. The approved brand name is Zynteglo. The marketing authorisation is more specific than the remit proposed in the scope and therefore we would suggest the wording is revised to: *To appraise the clinical and cost effectiveness of Zynteglo within its marketing authorisation for treating transfusion-dependent beta-thalassaemia (TDT) in patients 12 years and older who do not have a β0/β0 genotype, for whom haematopoietic stem cell transplantation is appropriate but a human leukocyte antigen matched related HSC donor is not available.*	Comment noted. The brand name has been amended in the scope. The population in the PICO table in the scope has been amended to reflect the age restriction of the technology's marketing authorisation. The remit has already been issued by the Department of Health and Social Care.
	Genetic Alliance UK	This is the standard wording	Comment noted.

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	UK Thalassaemia Society	The wording should be clearer in outlining who the target population is i.e. transfusion dependent patients over the age of 12 with some form of beta thalassaemia. The remit should be amended as follows: **To appraise the clinical and cost effectiveness of LentiGlobin within its marketing authorisation for treating transfusion dependent adolescents and adults with a form of β-thalassemia.**	Comment noted. The population in the PICO table in the scope has been amended to reflect the age restriction of the technology's marketing authorisation. The remit has already been issued by the Department of Health and Social Care.
Timing Issues	bluebird bio (company)	Current standard therapy in the majority of patients consists of chronic red blood cell (RBC) transfusions and iron chelation therapy, which are both burdensome and costly to the NHS and patients. The longer patients are treated with transfusions and chelation, the greater the risk of complications. TDT is also associated with a five-fold risk of mortality.	Comment noted.
	Genetic Alliance UK	The marketing authorisation was approved by the EMA at the end of May 2019 and given the serious nature of the condition it is vital the appraisal be carried out urgently so that there is no delay to patient access to this authorised medicine.	Comment noted.
	UK Thalassaemia Society	Studies published to date indicate that LentiGlobin offers a form of transfusion independence to thalassaemia patients who would not usually qualify for a hematopoietic stem cell transplant (HSCT) due to age or not having a HLA matched donor (Porter,2018) Studies have recorded that treatment with LentiGlobin increases haemoglobin which in turn reduces the overall frequency of transfusions (Porter, 2019).	Comment noted.

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		This not only decreases iron burden and comorbidities but also may result in an overall cost reduction to the NHS for hospital transfusion visits, iron chelation, inpatient stays and specialist clinics. There may also be a decrease in the demand for blood which will help with the current blood shortage observed by NHSBT. Not only could this novel treatment decrease some the physical complications due to thalassaemia, it could also improve the psychosocial aspects of living with the condition. The quality of life of patients and their families may also improve as the need for treatment and hospital visits may also decrease. At the moment, some patients and their families are required to take time off education and work to attend treatment days, clinics and other medical appointments. A reduction in transfusions and hospital stays could not only decreases iron related comorbidities but could offer patients the chance of experiencing a thalassaemia free life. This is a positive outcome for all parties involved and as a result we feel that access to this treatment should be prioritised as a matter of urgency.	
	Royal College of Pathologists/ British Society for Haematology	This therapy is not currently available hence this technology should be appraised soon so that patients can benefit	Comment noted.
Additional comments on the draft remit	bluebird bio (company)	Leading to this appraisal, there have been numerous discussions between bluebird bio, NICE and NHS England about the suitability of a Single Technology Appraisal (STA) for Zynteglo, as opposed to a Highly Specialised Technology (HST) Appraisal. We are concerned about the treatment being evaluated through STA but reluctantly accept the perspective of NICE, hoping that the committee will apply appropriate discretion to the complexity of the	Comment noted. The technology did not meet the topic selection criteria for the Highly Specialised

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		disease area, small trial populations and management of uncertainty. The HST committee apply a sliding ICER scale that enables greater willingness to pay for technologies which offer transformative QALY gains, but within STA the magnitude of the QALY gain does not adjust the assessment of value for money. bluebird bio does not feel the current ICER thresholds within STA enable recognition of the new approach and innovation that gene therapies bring as a one-time treatment with life-long benefits.	Technologies evaluation programme.
	UK Thalassaemia Society	The prognosis for TDT thalassaemia major patients living in the UK has been improved over the last 50 years. One main reason for the improvement has been the development of chelating agents which removes iron storage from the main organs. Up until recently, the only known cure for patients has been allogeneic hematopoietic bone marrow transplantation which was dependent on the patient having access to a suitable donor. With the introduction of gene therapy using the LentiGlobin drug product, the possibility for a cure will be extended to a wider range of patients. The UK Thalassaemia Society has always, during the forty years of existence as a registered group, encouraged and commissioned research which could improve the lives of patients and have been forefront in assisting with the development of most of the strides already marked in the evolution of treatment. We have also been able to celebrate being the country with the oldest surviving patients internationally and are looked upon to continue forging ahead. Towards this, therefore, we would like to support the submission of bluebird bio for the necessary approvals needed in this scoping exercise. We concur that this treatment is vital to those, wishing to have access to a possible cure, not considered before as they did not have the necessary HLA match for bone marrow transplant.	Comment noted.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	bluebird bio (company)	The background information only includes the number of patients with transfusion-dependent beta-thalassaemia major in the UK (813) which does not represent the population for which the Zynteglo marketing authorisation applies. For completeness, an estimate of the number of patients who would be eligible for treatment with Zynteglo within the target population would be necessary. Using genotype data from the Oxford Reference Molecular Haematology Laboratory and the Royal London Hospital, bluebird bio has estimated that 51% of β-thalassaemia patients in England harbour a non-β0/β0 genotype, equating to less than 322 prevalent patients. Considering a small proportion of patients not fit to undergo transplantation as well as a proportion of patients choosing not to receive treatment due to the need for myeloablative conditioning or risks of gene therapy, the actual patient pool eligible for Zynteglo per the licensed indication is expected to be 107. Also, in light of the capacity of treatment centres to provide the therapy, bluebird bio expects only a subset of these patients to undergo treatment per year. bluebird bio would also like to signify that despite improvements in iron monitoring and chelation therapy, TDT remains a life-limiting condition with significant morbidity, often presenting with endocrinopathies at an early age, and with organ toxicity (particularly the liver and heart) manifesting in middle-age. Recent analysis of the HES database suggests TDT is associated with a mortality rate more than five times greater than that observed in age/sex matched controls.	Comment noted. The background section of the scope is only intended to briefly describe the disease, prognosis associated with the condition, epidemiology and alternative treatments currently used in the NHS in England. The background section of the scope includes the liver and heart-related toxicities mentioned.
	UK Thalassaemia Society	The background information provided gives a good description of thalassaemia but does not mention what the criteria is for determining transfusion dependence. It is also not specific enough in identifying transfusion dependent patient. In addition, some beta thalassaemia major	Comment noted. The background section of the scope has been amended to: update the

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		and intermediate patients require life long blood transfusions in addition to those patients with Haemoglobin E disease also requiring red cell transfusions. Secondly, the figures quoted for the numbers of beta thalassaemia patients in the UK needs updating. As of May 2019, the figures for the number of patients living with any of the thalassaemia syndromes have been updated on the National Haemoglobinopathy Register. There are currently 1,380 people diagnosed with β-thalassemia in the UK of which 996 have beta thalassaemia major, 246 have beta thalassaemia intermedia and 138 have beta thalassaemia/Hb E disease. Thirdly, the background information in other parts of the world where thalassaemia is prevalent such as South America, the Caribbean and Africa has not been mentioned. The background information also does not mention the risks associated with having repeated transfusions in beta thalassaemia major. There is an increased risk of developing reactions due to alloimmunisation (allergic, haemolytic), bloodborne infections, graft versus host disease and the risk of developing transfusion related acute lung injury (Azarkeivan et al., 2011). Lastly, the background information does not take into consideration the risks involved with the repeated use of iron chelation medication such as kidney failure, ophthalmic and audiological deterioration, liver and heart toxicity, bone pain etc.	number of people in the UK with beta-thalassaemia major; include the additional countries suggested; include some risks of transfusions; include some risks of chelation therapy.
The technology/ intervention	bluebird bio (company)	No further comments beyond the naming of Zynteglo rather than LentiGlobin, as per the comments above in the 'Wording' section.	Comment noted. The brand name has been amended in the scope.

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	UK Thalassaemia Society	Yes	Comment noted.
Population	bluebird bio (company)	The population should be matched to the population covered by the marketing authorisation. Per the indication of Zynteglo, the treatment would be for people 12 years and older. Zynteglo is indicated for: *'Treatment of patients 12 years and older with transfusion-dependent β-thalassaemia (TDT) who do not have a β0/β0 genotype, for whom haematopoietic stem cell (HSC) transplantation is appropriate but a human leukocyte antigen (HLA)-matched related HSC donor is not available'.*	Comment noted. The population in the PICO table in the scope has been amended to reflect the age restriction of the technology's marketing authorisation. The remit has already been issued by the Department of Health and Social Care.
	UK Thalassaemia Society	No, we do not think that the target population has been addressed adequately. The population should include the target ages of the intended criteria (i.e. 12 and above) who do not have access to a HLA matched donor required for HSCT. The inclusion criteria for the intended population should stay within the ones identified in the trials as no safety data occurs out of this.	Comment noted. The population in the PICO table in the scope has been amended to reflect the age restriction of the technology's marketing authorisation. The remit has already been issued by the Department of Health and Social Care.

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Comparators	bluebird bio (company)	No further comments.	Comment noted.
	UK Thalassaemia Society	Apart from the comparators listed on the remit/ scoping document the current 'curative' treatment for transfusion dependent thalassaemia is HSCT, however, due to the difficulty in acquiring HLA matched donors and factors such as age and risks associated with transplant, many patients do not qualify for this form of treatment. Treatment with LentiGlobin may provide more patients the chance of acquiring curative treatment.	Comment noted. HSCT is not included as a comparator, as the marketing authorisation is for people who do not have a human leukocyte antigen (HLA)-matched related HSC donor. Therefore, treatment for people who have an appropriate donor for HSCT are not within the remit of this appraisal.
	Welsh Health Specialised Services Committee	Consider including the cost of treatment complications from iron overload and the cost of fertility preservation.	Comment noted.
Outcomes	bluebird bio (company)	To capture health system related benefits of Zynteglo, healthcare resource use should be added to the list of outcomes in the draft scope. Improvements in overall survival are being captured through the economic analysis rather than the clinical studies.	Comment noted.

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	UK Thalassaemia Society	The outcomes should also include the overall cost reduction to the NHS with reduced blood transfusions and the reduction in demand of blood stocks placed on the NHSBT.	Comment noted.
Economic analysis	bluebird bio (company)	The draft scope indicates that the perspective on costs is that of UK National Health Service and Personal Social Services (PSS). However, there is a high burden of disease in terms of societal costs for both the patient and family members. For those of working age, patients may have reduced working hours or are unable to work due to their regular transfusions or complications of iron overload. Attending school can also be challenging for TDT patients as a result of the burden of treatment, which includes long transfusion times, repeated every 2-5 weeks. Additionally, most services do not provide planned care (transfusions, blood tests, clinic visits) outside normal working/school hours and this leads to patients missing on average 1.5 to 2 days of education or work per month. Family members acting as carers for patients with TDT may reduce their working hours, change their job, or be unable to work altogether. As a consequence of these substantial costs that fall outside of the NHS & PSS perspective, the model will underestimate the potential value of Zynteglo for patients and their families if the NHS and PSS perspective only is considered. Given the above, Zynteglo is likely to have financial benefits for government bodies other than the NHS and thus, as per the NICE methods guide, we wish to request that the remit of the appraisal considers these elements. Specifically, consideration of substantial benefits (5.1.10) and cost savings (5.1.11) to other government bodies, costs borne by patients when reimbursed by NHS or PSS (5.5.12) and costs arising from care by family members, friends or a partner which could otherwise have been provided by the NHS or PSS (5.5.13). If Zynteglo were reviewed under the HST process, the committee would usually consider any non-NHS costs but within the STA framework this is not a routine consideration. bluebird bio feel that such	Comment noted. Sections 5.5.11-5.5.13 of the Guide to the methods of technology appraisal 2013 outline the Committee's approach to non-NHS and PSS costs, while sections 5.6.1-5.6.3 outline the approach to discounting in the reference case. In particular, section 5.6.3 indicates that a discount rate of 1.5% for costs and benefits can be presented as sensitivity analyses. Further information is given in section 6.2.19, about the circumstances where non-3.5% discount rates may be considered by Committee. 'In cases when treatment restores people who

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		considerations are essential in order to conduct a holistic assessment of the value for money for a one-time gene therapy with the potential for lifelong benefit in a rare disease. We request that these non-health factors are included within the scope such that the committees can consider its social value judgements in decision making, as per section 6.2.20 of the guidelines. The NICE reference case indicates that the perspective on outcomes is that of the patient and, where relevant, caregivers. As indicated above, TDT places a burden on caregivers which is important to capture in terms of utilities. The impact on caregivers has been quantified in a UK chart review study which included HRQoL measures, being conducted by bluebird bio in collaboration with treating NHS centres. The model therefore captures outcomes for both the patient and their caregivers. Regarding the discount rate applied to the economic analysis, a differential discounting approach will be proposed, applying an annualised 3.5% discount rate to costs and 1.5% discount rate to health outcomes (QALYs). This better reflects the utility where treatment is transformative, and the survival benefits are gained over a long period. It contrasts to a non-differential discount rate where present outcomes are more heavily weighted when assessing the impact of therapies. The use of differential discounts is aligned with the most recent UK HM Treasury Green Book, which specifies that differential discount rates should be used for costs and outcomes, and that a 1.5% discount rate should be used for all health outcomes.	would otherwise die or have a very severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years)'…A discount rate of 1.5% for costs and benefits may be considered by the Appraisal Committee if it is highly likely that, on the basis of the evidence presented, the long-term health benefits are likely to be achieved. Further, the Appraisal Committee will need to be satisfied that the introduction of the technology does not commit the NHS to significant irrecoverable costs.'
	UK Thalassaemia Society	Research published by Karnon et al (1999) estimates the lifetime costs of a beta thalassaemia patient to be approximately 803,002 pounds sterling whereas research published by Weidlich et al (2016) based on 2013 costs, estimates lifetime costs without any comorbidities to be around 483,545 pounds sterling.	Comment noted.

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		Based on the disparity across both studies and the impact of UK's departure from the European Union, it is difficult to comment what the potential costs of treatment for transfusion dependent beta thalassaemia major patients will be. The data shows a reduction in transfusion volume and frequency, which will reduce the demand place on NHSBT and the NHS over time.	
Equality	bluebird bio (company)	No issues relating to equality have been identified.	Comment noted.
	Genetic Alliance UK	It should be taken into account that transfusion-dependent beta-thalassaemia mainly affects those from Mediterranean, South Asian, South East Asian and Middle Eastern descent.	Comment noted. These populations are listed in the background section of the scope. Issues related to differences in prevalence or incidence of a disease cannot be addressed in a technology appraisal.
	UK Thalassaemia Society	none	Comment noted.
Other considerations	bluebird bio (company)	No further comments.	Comment noted.
	UK Thalassaemia Society	The risks associated with HSCT that have not been included in the scoping document.	Comment noted. HSCT risks are not included, and HSCT is not included as a comparator, as the

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			marketing authorisation is for people who do not have a human leukocyte antigen (HLA)-matched related HSC donor. Therefore, treatment for people who have an appropriate donor for HSCT are not within the remit of this appraisal.
Innovation	bluebird bio (company)	Zynteglo is a highly innovative technology which represents a 'step-change' in the treatment paradigm owing to the ability of Zynteglo to address the underlying cause of the condition using the patient's own haematopoietic stem cells i.e. an autologous treatment approach. Zynteglo is expected to offer lifelong benefit in those patients that successfully achieve transfusion-independence and is therefore disease-modifying by negating the need for chronic RBC transfusion therapy and the resultant, inevitable iron overload that ensues in patients managed with standard-of-care. Consequently, Zynteglo offers the potential to transform the quality of life of patients over their whole lifetime, including the mitigation of disease and treatment related complications, and prolonging survival. Zynteglo has been granted orphan drug designation by the European Medicines Agency (EMA). Zynteglo received Promising Innovative Medicine (PIM) designation from the MHRA in October 2015. It is a novel gene therapy and is certified as an advanced therapeutic medicinal product (ATMP) by the EMA. The Government recognises ATMPs as a revolution in medicine that allow a patient's cells and tissues to be engineered to restore normal function.	Comment noted.

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	Genetic Alliance UK	LentiGlobin represents a step-change in the treatment of transfusion-dependent beta-thalassaemia in that the only other curative intervention (stem cell transplant) is inherently risky and can result in death. Lentiglobin, according to clinical trials, allows the patient to achieve sustained periods of transfusion independence which could represent a significant improvement in a patient's quality of life.	Comment noted.
	UK Thalassaemia Society	Yes, the UKTS considers the technology to be novel. The trial data published on the mechanisms of LentiGlobin could provide a possible reduction in blood transfusion requirements and associated iron overload.	Comment noted.
	Welsh Health Specialised Services Committee	Yes – it is a very promising treatment option. We wonder whether this should be offered as frontline treatment rather than reserve it for people who don't have a matched donor for transplant, since transplant renders recipients infertile - a complication that could be avoided with gene therapy.	Comment noted. Use of the technology in this way is outside its current marketing authorisation.
Questions for consultation	bluebird bio (company)	All questions in the draft scope document have been covered in the sections above.	Comment noted.
	UK Thalassaemia Society	No	Comment noted.
Additional comments on the draft scope	bluebird bio (company)	bluebird bio is in discussions with NHS England regarding the requirements and activities that treatments centres in England will need to provide, in order to deliver an effective and auditable service that ensures safe and effective delivery of Zynteglo. bluebird bio would like NICE to take into account the	Comment noted. NICE will receive a submission from NHS England as part of the appraisal, and will

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		service specification design and procurement requirements under development.	maintain contact with NHS England during the appraisal to receive updates on proposed service specification design and procurement requirements within the NHS.
	Genetic Alliance UK	For the following reasons we consider the therapy more suited for the Highly Specialised Technology (HST) evaluation programme. When taken together, the criteria create a narrow group of conditions, treatments and services that must be aligned to offer access to a much more fruitful evaluation pathway. While population affected is a clear criterion that can be considered unbiased or fair, other criteria are much less easy to consider as fair. We wish to draw attention to three HST criteria which we believe patients with β0/β0 genotype might consider themselves to be unfairly treated with respect to other patients with rare conditions who have accessed the HST route. 1) The existence of current treatment ruling out definition of the condition as chronic and severely disabling: Just because a condition happens to have a reasonably effective treatment should not prevent a future treatment being selected for the HST pathway. In this sense a patient with β0/β0 genotype thalassaemia might consider themselves discriminated against because of the existing treatment. 2) The arrangements for commissioning this treatment within the NHS: The commissioning arrangements for most rare disease services are the result of historical custom and practice. Very few specialised services have been significantly altered in the past six years since the advent of NHS England,	Comment noted. The technology did not meet the topic selection criteria for the Highly Specialised Technologies evaluation programme.

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		and hardly any new Highly Specialised Services have been delivered around the advent of a new medicinal product, as has been custom prior to 2012. The slow rate of renewal of specialised commissioning in England means that there is little chance of a service being altered to take account of new treatment paradigms. Additionally, the design of Advanced Therapy Treatment Centres is a strong indication that all gene therapies will be delivered in a small number of centres which is analogous to a highly specialised service. In this sense a patient with β0/β0 genotype thalassaemia might consider themselves discriminated against because of historical commissioning arrangements that our out of their control. 3) The target patient group is distinct for clinical reasons: This is a well discussed criteria for which exceptions have been made in the past (cf nonsense mutation Duchenne muscular dystrophy). In many clinics in England β0/β0 genotype thalassaemia is considered distinct from other genotypes, in that it is a different genotype. Clinical trials have shown the treatment to be effective in this group, and not in the other. In this sense a patient with β0/β0 genotype thalassaemia might consider themselves discriminated against because their clinical differences (established in clinical trial) are outside the outdated definitions used in the HST criteria.	

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope:

Novartis (comparator).